REMARKS

Claims 27-39 are currently pending. These claims replace new claims 27-39 of the Amendment submitted by Applicants on August 9, 2006, and are submitted in response to the Notice.

The basis for alleged non-compliance is as follows. The claims elected, in response to a restriction requirement, contained a preamble which referred to a Cystic Fibrosis Trans-membrane conductance Regulator (CFTR) polypeptide (*e.g.*, claim 17) which could, according to certain dependent claims (*e.g.*, claim 19) comprise an internalizing peptide, whereas the new claims submitted on August 9, 2006 contained a preamble referring to a "transport-enhancing polypeptide." The Examiner contends that this revision of the preamble changed the subject matter of the claims to a non-elected invention. Applicants respectfully disagree. Applicants assert that the new claims *do not* represent a distinct invention, because the elected claims (including, for example, claims 17 and 19) *function* as transport-enhancing polypeptides. The language was changed because in all the new claims an internalizing peptide is required; since the internalizing peptide does not derive from the CFTR gene it seemed, to Attorneys for Applicants, desirable not to refer to these "hybrid" polypeptides as CFTR polypeptides. Since the function of the elected peptides is to enhance ion transport, the preamble was revised to refer to a "transport enhancing polypeptide."

This rationale was discussed with the Examiner in a telephonic interview after the Notice was received by Attorneys for Applicants, but the Examiner was not persuaded to withdraw the Notice. Therefore, while not admitting that the claims submitted August 9, 2006 referred to a different invention, Applicants revise the claims to obviate the basis for the Examiner's objection. The new claims simply refer to a "polypeptide," which can accurately

refer to a polypeptide that comprises a portion derived from the CFTR gene as well as an internalizing peptide.

Because the Amendment submitted August 9, 2006 contained reference to the language of the new claims throughtout its text, all sections of that amendment are included in this document.

The Examiner has rejected claims 17-23 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement and as being unenabled. The Examiner has rejected Claims 17-23 under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner has also rejected Claims 17-23 under 35 U.S.C. § 101 as directed toward non-statutory subject matter. The Examiner has rejected Claims 17, 18 and 21 under 35 U.S.C. § 102(b) as anticipated by Meacham et al., 1999, The Hdj-2/Hsc70 chaperones pair facilitates early steps in CFTR biogenesis, EMBO J. 18(6): 1495-1505, ("Meacham et al."). Furthermore, the Examiner has rejected Claims 19, 20, 22 and 23 under 35 U.S.C. § 103(a) as obvious over Meacham et al. in view of Robbins et al. (U.S. Patent No. 6,881,825 filed August 31, 2000) ("Robbins et al."). For the reasons detailed below, the rejections should be withdrawn and the claims should be allowed to issue.

The Claims Comply With The Written Description Requirement

The Examiner has rejected claims 17-23 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner contends that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Examiner alleges that the claims are directed to a genus of Cystic Fibrosis Trans-membrane conductance Regulator (CFTR) polypeptide molecules comprising amino acid sequences capable of binding to a molecular chaperone and enhancing CFTR channel activity in a cell expressing any mutant CFTR with no defined structure of the CFTR polypeptide, cell type where expressed, or type/specificity of the mutation. The Examiner further alleges that the specification discloses a single CFTR polypeptide, and does not describe the structure and/or function of all CFTR polypeptides of the genus having the desired characteristics. The Examiner contends that the disclosure of a single CFTR polypeptide is not representative of the entire genus, and therefore the inventors did not have possession of the invention as claimed.

The claims as presently amended address the basis for the rejection. As recited in new claim 27, the invention encompasses a polypeptide comprising an internalizing peptide operably linked to a CFTR polypeptide having a deletion of amino acid residue 508 of a 1480 amino acid wild type CFTR protein. As set forth in new claim 35, the invention encompasses a polypeptide comprising a CFTR polypeptide comprising the nucleotide binding domain 1 (NBD1) and regulatory (R) domains of human wild type CFTR, as well as an internalizing peptide. Support for new claims 27 and 35 may be found in the specification at paragraph 35, lines 3-12; and paragraph 36. Applicants assert that the new claims obviate the basis for the rejection, which should be removed.

The Claims are Enabled

The Examiner has rejected claims 17-23 under 35 U.S.C. § 112, first paragraph, as being unenabled. The Examiner states that the specification "does not reasonably provide enablement for any Cystic Fibrosis Trans-membrane conductance Regulator (CFTR) polypeptide molecules comprising amino acid sequences capable of binding to any molecular chaperone and enhance CFTR channel activity in any cell type expressing any mutant CFTR with no defined structure of the CFTR polypeptide, cell type where expressed or type/specificity of the mutation."

Applicants assert that the claims as currently amended are enabled by the specification. As recited in new claim 27, the invention encompasses a polypeptide comprising an internalizing peptide operably linked to a CFTR polypeptide having a deletion of amino acid residue 508 of a 1480 amino acid wild type CFTR protein. As set forth in new claim 35, the invention further encompasses a polypeptide comprising a CFTR polypeptide comprising the nucleotide binding domain 1 (NBD1) and regulatory (R) domains of human wild type CFTR, as well as an internalizing peptide. Support for new claims 27 and 35 may be found in the specification at paragraph 35, lines 3-12; and paragraph 36.

Applicants assert that based upon the disclosure in the specification and the knowledge of a person of ordinary skill in the art at the time of filing, the specification is enabling for the use of the claimed CFTR polypeptide to enhance CFTR channel activity when present in a cell expressing a mutant CFTR. As shown in the specification at paragraphs 78-79, and 85-87, administration of the claimed CFTR polypeptide to cells comprising mutant CFTR increased CFTR channel activity in the treated cells as measured by an increase in chloride

permeability of the treated cells (paragraph 78, 79, and Figure 7B). Applicants further assert that treatment of the mutant cells with the claimed CFTR polypeptide also increased CFTR expression in the mutant cells as shown in the specification at paragraphs 85-87, and Figure 9A.

The presently amended claims are further enabled by the specification which demonstrates a mechanism by which the claimed CFTR polypeptides can increase CFTR channel activity. As stated in the specification at paragraph 8 and 81, mutations in CFTR, for example, the deletion of amino acid residue 508, causes the retention and degradation of mutant CFTR in the endoplasmic reticulum (ER). As a result, the CFTR cannot escape the ER to form functional channels. This retention and degradation is postulated to be mediated by the association of the mutant CFTR with the chaperones Hsc/Hsp70 and Hdj-2. As shown in the specification at paragraphs 82-84, CFTR polypeptides, as encompassed by claims 17 and 33, reduce the association of Hdj-2 with mutant CFTR, which would otherwise lead to degradation of the mutant CFTR. By reducing the association with Hdj-2 in the ER, the CFTR polypeptides enhance and promote the release of mutant CFTR from the ER, providing a mechanism for the increase in CFTR channel activity previously described in the treatment of mutant cells.

Applicants assert that the specification is sufficiently enabling for a person of ordinary skill in the art to practice the invention within the scope of the presently amended claims, specifically to utilize the CFTR polypeptides to enhance CFTR channel activity in a cell with a mutant CFTR. Accordingly, Applicants request withdrawal of the rejection.

The Claims are Definite

The Examiner has rejected Claims 17-23 under 35 U.S.C. § 112, second paragraph, as indefinite. The Examiner alleges that the claims fail to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The Examiner contends that claim 17 recites the indefinite abbreviation "CFTR" when describing Cystic Fibrosis Trans-membrane conductance Regulator (CFTR). Applicants have amended the claims to remove the abbreviation "CFTR," and recite the full name "Cystic Fibrosis Trans-membrane conductance Regulator." The Examiner further contends that it is unclear what sequences comprise the single CFTR polypeptide of claim 17. Applicants have amended the claims to refer to a wild type Cystic Fibrosis Trans-membrane conductance Regulator protein having 1480 amino acids. The amino acid sequence of wild type CFTR is well known, as described in the specification at paragraph 36, and in Sheppard et al., 1999, Structure and function of the CFTR chloride channel, Physiol. Rev 79:S23-45 (Submitted in the Information Disclosure Statement filed March 18, 2004). The Examiner further rejects claims 18-23 as being dependent on the base claim 17, and not correcting the defect in claim 17. As the amended claims are definite, as described above, and all claims depending from the amended claims are also definite, Applicants request that the rejection be withdrawn.

The Claims are Directed to Statutory Subject Matter

The Examiner has rejected Claims 17-23 under 35 U.S.C. § 101 as directed toward non-statutory subject matter. The Examiner contends that the claims read upon naturally occurring proteins and/or nucleic acids, which is non-statutory subject matter. Applicants have amended the claims to refer to polypeptides comprising an isolated Cystic Fibrosis Trans-membrane conductance Regulator (CFTR) polypeptide as well as an internalizing peptide, which are not found in nature. Thus, Applicants request that the rejection be withdrawn.

The Claims are Novel

The Examiner has rejected Claims 17, 18 and 21 under 35 U.S.C. § 102(b) as anticipated by Meacham et al. Meacham et al. describes CFTR and a CFTR polypeptide lacking amino acid residue 508 binding the chaperones Hdj-2 and Hsc70. Meacham et al. further discloses that NBD1 is necessary for the binding of CFTR polypeptides to the chaperones. Additionally, Meacham et al. discloses binding of chaperones Hdj-2 and Hsc70 by CFTR polypeptides comprising sub-domains of the CFTR protein.

The Examiner contends that Meacham et al. discloses a CFTR polypeptide comprising two membrane-spanning domains, two nucleotide binding domains, and a regulatory domain that bind the chaperones Hdj-2 and Hsc70. The Examiner further contends that Meacham et al. describes CFTR polypeptides comprising the Δ508 mutation that binds the chaperones Hdj-2 and Hsc70.

Applicants assert that Meacham et al. does not anticipate the invention as claimed by the amended claims. The claimed invention encompasses a CFTR polypeptide comprising an internalizing peptide. Meacham et al. transfects cells with nucleic acid molecules encoding

CFTR polypeptides that do not comprise an internalizing peptide. Because the claimed CFTR polypeptides of the invention are different than the CFTR polypeptides of Meacham et al., Applicants assert that Meacham et al. does not anticipate the amended claims, so that the rejection should be removed.

The Claims are Not Obvious

The Examiner has rejected Claims 19-20 and 22-23 under 35 U.S.C. § 103(a) as obvious over Meacham et al. in view of Robbins et al. Meacham et al. discloses CFTR polypeptides that bind Hdj-2 and Hsc70, as described above. Robbins et al. describes internalizing peptides that can facilitate uptake and transport into the cytoplasm of a cell, both *in vivo* and *in vitro*. Robbins et al. discloses a number of internalizing peptides, including those of SEQ ID NOS: 1-3 of the instant application. The Examiner contends that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Meacham et al. and Robbins et al. to more efficiently express the CFTR polypeptides of Meacham et al. by incorporating the internalizing peptides of Robbins et al.

Applicants disagree with the Examiner, and assert that the claims are not obvious over Meacham et al. in view of Robbins et al. considered separately or in combination. To establish a *prima facie* case of obviousness, all the claim limitations must be taught or suggested by the prior art (*In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974). *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494,496 (C.C.P.A. 1970) states that "All words in a claim must be considered in judging the patentability of that claim against the prior art." The Examiner must also meet three criteria. The Examiner must establish that (1) there is some

suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there is a reasonable expectation of success; and (3) the prior art reference (or references when combined) teach or suggest all the claim limitations. See M.P.E.P. §§ 706.02(j) and 2143. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, rather than Applicants' disclosure.

Applicants assert that there would be no motivation to combine the teachings of Meacham et al. and Robbins et al. Meacham et al. describes transfecting cells *in vitro* with nucleic acids encoding CFTR polypeptides in order to study the polypeptides' chaperone binding characteristics as the polypeptides pass through the ER following translation. Robbins et al. discloses internalizing peptides used to transport a cargo, for example, a protein, into the cytoplasm of a cell. Meacham et al. transfects cells with nucleic acids encoding CFTR polypeptides. The nucleic acids of Meacham et al. are only translated into CFTR polypeptides after they have been introduced into the cells. Applicants respectfully remind the Examiner that "the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination" (*In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (FED. Cir. 1990); and M.P.E.P. § 2143.01(III)). Meacham et al. internalizes nucleic acids encoding CFTR polypeptides, not the CFTR polypeptides themselves. Adding Robbins et al.'s internalizing peptide to Meacham et al.'s CFTR polypeptides would not affect internalization since it is a nucleic acid that is internalized in Meacham et al. The internalizing peptide, like the CFTR polypeptide, would be translated inside the cell after the nucleic acid has already been internalized. Thus, there would be no motivation to combine the teachings of the two references.

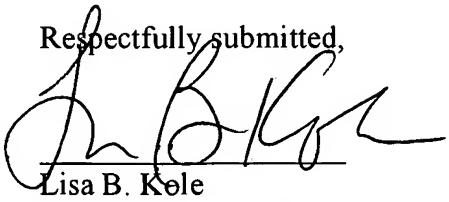
Furthermore, Applicants assert that the enhancement of CFTR channel activity by the claimed CFTR polypeptides is an unexpected result that could not have been predicted by the combination of Meacham et al. and Robbins et al. Although Meacham et al. discloses the binding of CFTR polypeptides to chaperones, Meacham et al. does not teach or suggest an increase in CFTR channel activity. At most, if, for the sake of argument, Meacham et al. and Robbins et al. were combined, the expected result would be that the internalized peptides would engage in chaperone-mediated folding. The increase in CFTR channel activity is an unexpected and novel consequence resulting from the use of the CFTR polypeptides encompassed by the presently amended claims.

For the reasons present above, Applicants believe the amended claims are not obvious in view of Meacham et al. or Robbins et al. considered singly or in combination. Thus, Applicants request the rejection be removed.

CONCLUSION

Applicants believe that the claims are in condition for allowance. Withdrawal of all rejections and reconsideration of the amended claims is requested.

Respectfully submitted,



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